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UPDATE

Highlights of Current and Future Directions Related to Alternative Test Method Activities and Research and Development

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Note

- Thanks to EPA's Office of Research and Development for providing some of the slides used in this presentation.

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EPA- ICCVAM Partnership

- Active Partnership since ICCVAM's inception in 1994
- EPA recognized early on:
  - the importance of working together with other federal agencies towards the goal of advancing the principles of the 3Rs (reduction, refinement, replacement of animal use) while
  - doing so in the context of the Agency's mission to protect human health and the environment and to promote high quality science
- EPA has benefited from the thoroughness of ICCVAM analyses and the usefulness of information on test method strengths, limitations, accuracy, reliability, and applicability domains

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EPA-ICCVAM Previous/Ongoing Collaborations

- Guidance and validation issues
- Performance standards for alternative test methods
- Interactions with OECD test guidelines program
- Participation on intra-U.S. and international working groups, task forces and workshops
- Follow-up on EPA's nominations for ICCVAM/NICEATM evaluation

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ICCVAM-EPA Collaborations: Recent Activities

- Ongoing activities with ICCVAM/NICEATM to explore scope expansion for Local Lymph Node Assay (LLNA) and ocular irritation and corrosion assessments
- Nomination letter sent to ICCVAM/NICEATM by EPA (OPP/OPPTS) requesting a technical review of a non-animal approach to determining eye irritation potential for hazard labeling of antimicrobial cleaning products
- Agency also plans to provide funding for formation of an ILAR/NAS workgroup to update guidance on humane care and use of animals in toxicology and safety assessment
- Center for Alternatives to Animal Testing (CAAT)– Participation on Advisory Board and in upcoming symposium on developmental neurotoxicity alternative testing

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Strategic Plan Development

- EPA established an agency-wide Future of Toxicity Testing Workgroup (FTTW) to develop a response to the recommendations in the National Research Council 2007 report on *Toxicity Testing in the 21st Century: A Vision and a Strategy*

- The FTTW developed a Strategic Plan for the future of toxicity testing at EPA

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Strategic Plan Development

Components of the plan include a number of strategic goals involving:

- Toxicity Pathway Identification and Chemical Screening and Prioritization
- Toxicity Pathway-Based Risk Assessment
- Institutional Transition
- Applications and impacts of, as well as drivers for, the proposed new approaches

- Computational toxicology approaches featuringToxCast™ and including toxicity pathway and knowledgebase development are key aspects of the plan
- The plan has recently received endorsement by the Agency's Science Policy Council
- The plan is seen as a critical initial step in a long range process to move forward with a strategy for a toxicity testing paradigm shift at the Agency

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Interagency Collaboration

- The EPA Strategic plan will serve as a vehicle for discussions with other federal agencies- such as those EPA is partnering with (NTP/NIEHS, NCGC/NIH) in a Memorandum of Understanding (MOU) to leverage resources and expertise and strengthen collaborations on High Throughput Screening, Toxicity Pathway Profiling, and Biological Interpretation of Findings

- As part of collaborations between federal agency partners involved in the MOU, four working groups have been established, involving:
  - Chemicals
  - Pathways and Assays
  - Informatics
  - Targeted Testing
  - Apparently a goal has just been established to obtain about 6000 chemicals at NCGC and to start screening them in a near-future time frame

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Toxicity Testing in the 21st Century


THE NATIONAL ACADEMIES

REPORT IN BRIEF

July 2007

Toxicity Testing in the 21st Century: A Vision and a Strategy

THE NATIONAL ACADEMIES

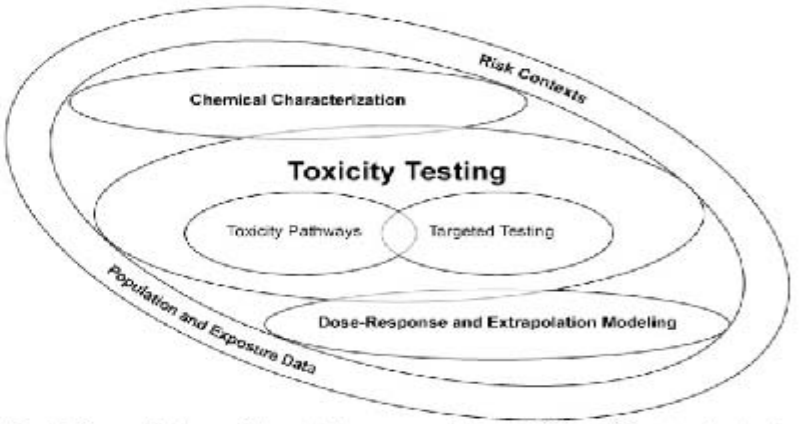

Figure 1. The committee's vision for toxicity testing as a process that can include chemical characterization, toxicity testing, and dose-response and extrapolation modeling as part of broader agency decision-making.

Modified from NRC, 2007

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Developing a New Approach

There are many reasons for development of new approach to toxicity testing, including:

- Part of Agency follow-up to NRC reports

- Need to obtain information and address information gaps for chemical hazard and risk assessment for many different Agency programmatic needs (e.g., for different exposure scenarios, to understand mechanisms of action/toxicity, for life stage sensitivity issues, to aid in mixtures clean-up, for species extrapolation)
  - For many, many chemicals (thousands) in many classes
  - Exploit recent advances in high throughput screening and toxicogenomics
  - Statutory authority differences
  - Cost of conventional approaches
  - Reduce animal use where possible
  - Need for better information for human and ecological risk assessment
  - Need to reduce uncertainties in hazard and risk assessment where possible
- While using best available science for decision making

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ToxCast™

- ToxCast™ - Uses a variety of high throughput screening (HTS) assays/techniques to derive chemical profiles (signatures) for hundreds of endpoints (e.g., with potential relevancy for carcinogenicity, reproductive toxicity, developmental toxicity, neurotoxicity, chronic toxicity)

- www.epa.gov/comptox/toxcast - linkage with EPA ORD's computational toxicology program (NCCT- National Center for Computational Toxicology)
- Potential Utility (e.g.):
  - Characterization of toxicity pathways
  - Use resulting hazard predictions for screening and priority setting for further testing
  - Obtain mechanism of action information
  - Data sharing with other stakeholders nationally and internationally
  - Public accessibility of data
  - Obtain data for predictive modeling and targeted testing
- Relational Database Development (ToxRefDB) to house information for *in vivo* data comparisons/linkage and development of other data management tools (e.g., ACTor, DSSTox)

High-Throughput Screening Assays

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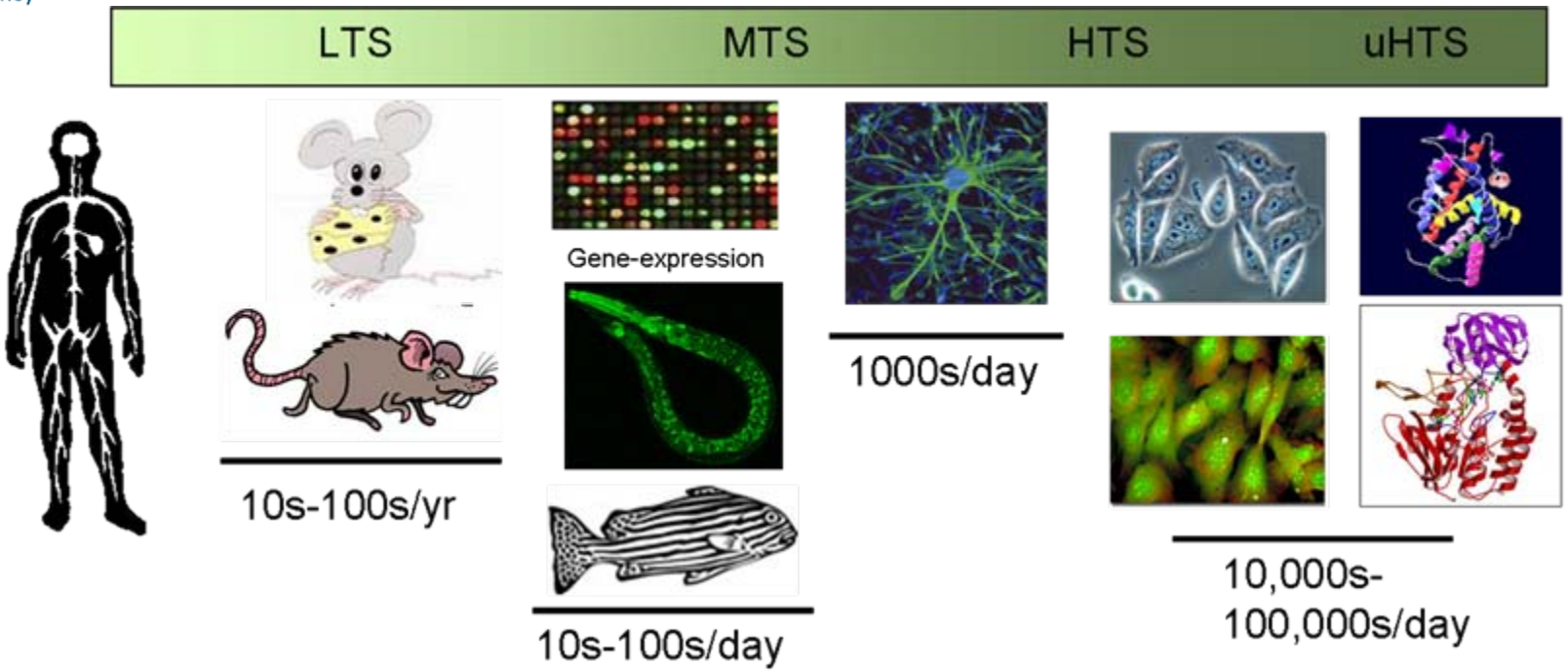

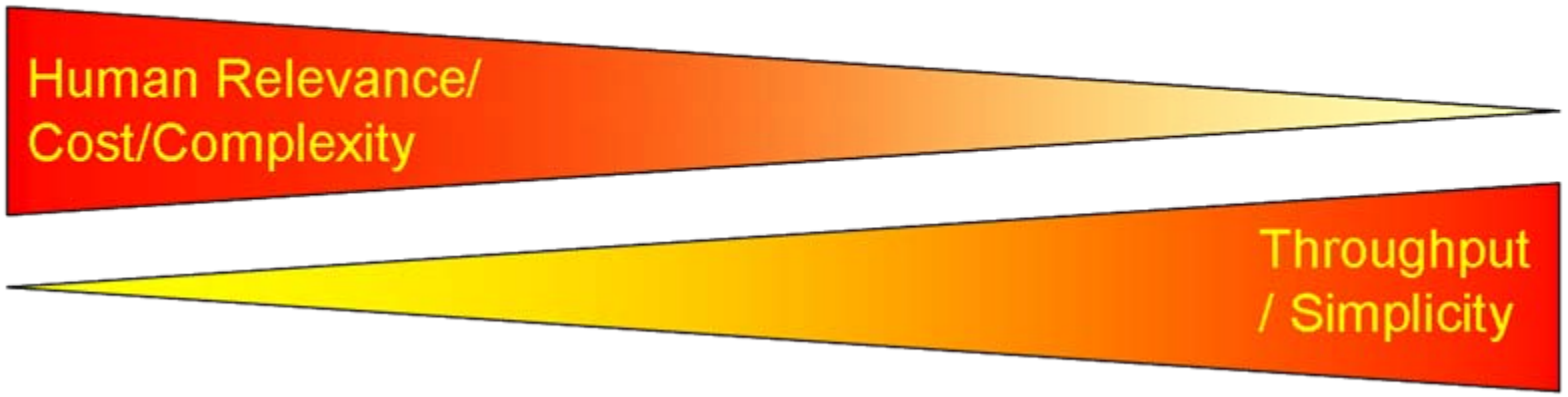

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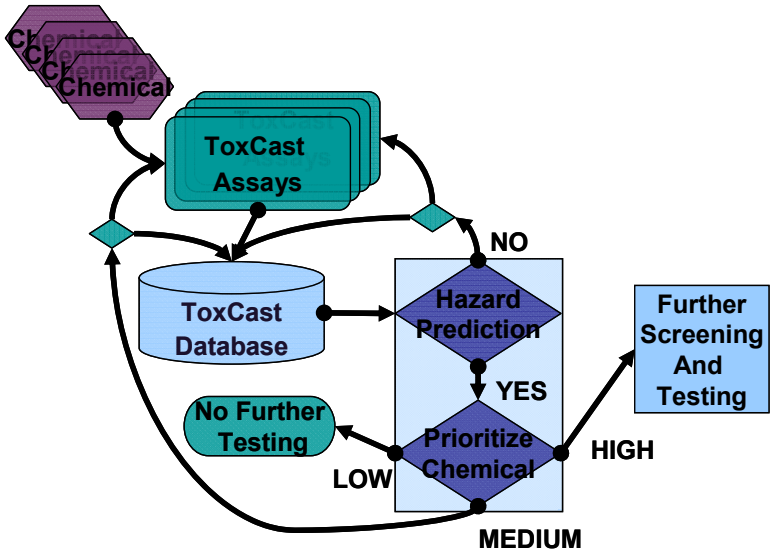
Phased Development of ToxCast

Phase	Number of Chemicals	Chemical Criteria	Purpose	Est. Cost per Chemical	Date
I	>300	Data Rich (pesticides)	Signature Development	$20k	FY07-08
II	>1000	Expanded Structure and Use Diversity	Evaluation and Extension	$12-15k	FY08-09
III	Thousands	Data poor	Prediction and Prioritization	$6-10k	FY09-12



- Deliver an affordable, science-based system for categorizing chemicals
- Increasing confidence as database grows
- Identify potential mechanisms of action
- Refine and reduce use of animals in hazard identification and risk assessment

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Information Management

- **ACToR**: Centralizes many types and sources of data on environmental chemicals derived from more than 150 sources
- **ToxRefDB:** Compiles in vivo toxicology data for ToxCast with current focus on all relevant data from data evaluation records on 280 food-use pesticides from OPPTS
- **DSSTox:** Curates chemical structure and related assay data with its web site providing a publicaaly available forum for publishing downlaodable chemical structure files
- **Genomics Data Management:** Relies on Array Track to house genomics data from ORD labs
- **BDSM:** Reference collection of gene-expression data for modeling animal development

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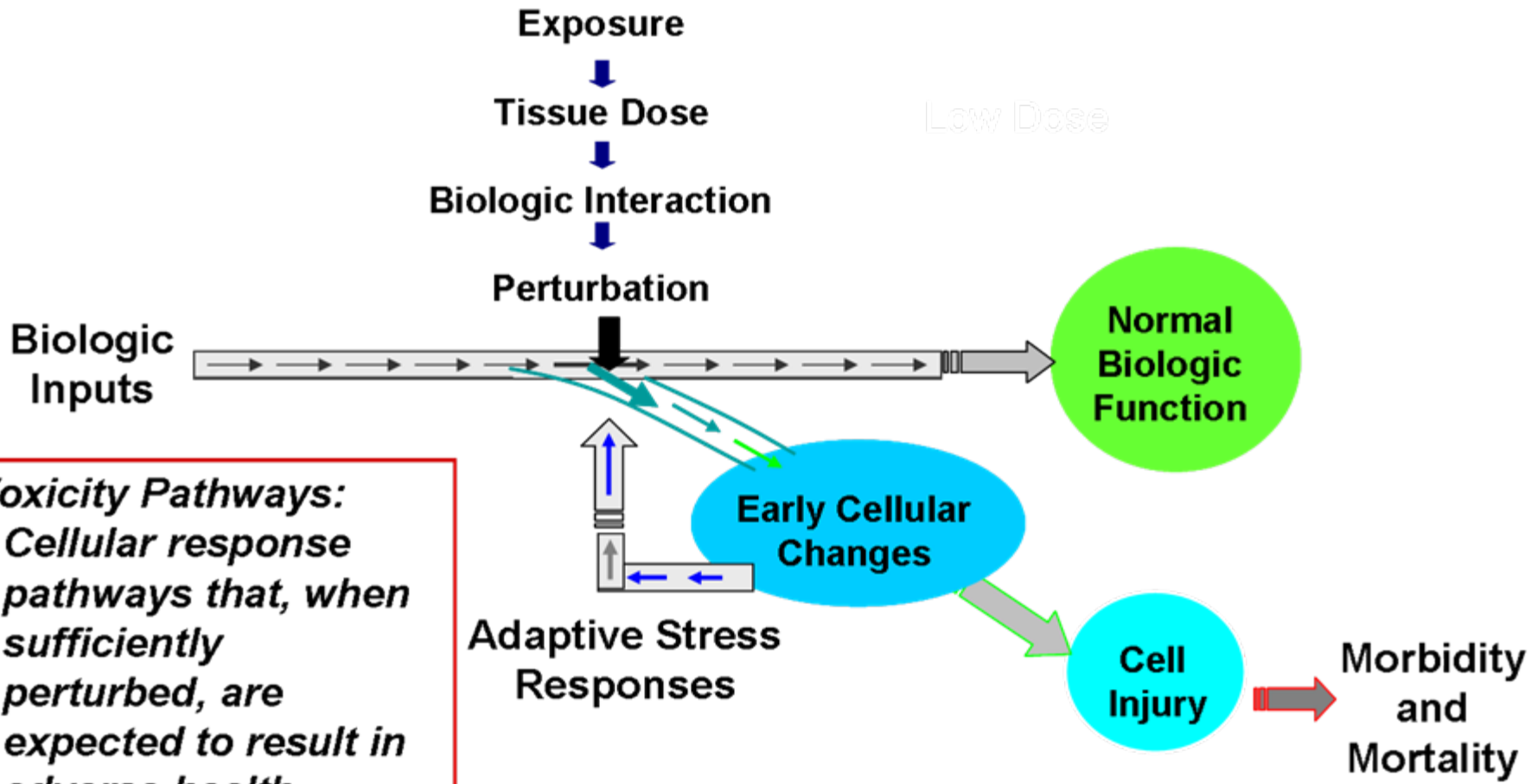
Toxicity Pathway Elucidation- Example of Expected Utility

- Use of computational techniques and models to predict/estimate toxicity pathway based risk
  - Development of virtual tissues, organs and systems with goal of linking exposure, dosimetry and response (simulation of molecular processes) to predict potential effects
  - Example: Virtual Liver Project – prediction of liver injury by chemicals

"Transformative Paradigm Shift" → Focus on Toxicity Pathways



Toxicity Pathways: Cellular response pathways that, when sufficiently perturbed, are expected to result in adverse health effects.

Anderson,M. 2005

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Moving Forward with the Vision

- Addressing inevitable challenges in vision development, implementation, integration and acceptance
  - Iterative, long-term
  - Complexities of data analysis and interpretation
  - Adequacy of new approaches in meeting regulatory needs and relative to existing approaches
  - Expertise and training
- Some Considerations
  - Availability of comprehensive suites of *in vitro* tests
  - Availability of targeted tests to ensure adequate data for decision-making
  - Models of toxicity pathways to support application of in vitro test results to predict general population exposures
  - Infrastructure changes to support research
  - Funding
  - Outreach to stakeholders
  - Validation issues/challenges for (rapidly) evolving technologies and complex (e.g., layered, multi-leveled) test strategies and systems for use in the regulatory arena

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Acceptance and Application of New Science: Recasting the Context for Validation

"despite the established value of in vitro systems… increased reliance on them for regulatory testing may require further evidence of validity."

"… because validation assesses fitness for a purpose, such exercises should be judged with the specific intended purpose in mind."

NRC, 2007

Application and Acceptance of New Science: Numerous Perspectives on Validation

ICCVAM and OECD Guidance refer to internal and external validation as applied to the development of methods

NAS *Applications of Toxicogenomic Technologies to Predictive Toxicology and Risk Assessment*

- Platform validation
- Software/data analysis validation
- Biologic validation
- Generalizability
- Regulatory validation

NAS Toxicity Testing in the 21st Century

- Pathway Knowledge Validation
- Assay Development and Validation
- Assay Relevance and Validity Trial
- Test Batteries Validation

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Substantiating Prediction Chains at Progressive Levels- some thoughts

Example: Progression of Information levels that seek to build on one another (are links from one prediction level ( ) to next adequately substantiated?)

Data from “omics” technologies
↓ (1)
Gene expression changes
↓ (2)
Biochemical pathways
↓ (3)
Toxicologic effect
↓ (4)
Relevance for human health or the environment

Modified from Corvi, R. et al, EHP Volume 114 (3) pp. 420-427 (2006).